REMARKS

Status of the claims

In the Response submitted April 28, 2010, claims 1-8 and 10-85 were pending of which 1, 6-8, 10-33, and 71-75 were rejected and claims 2-5, 34-70, and 76-85 were withdrawn. Applicants amended pending claims 1, 6-8, 11-13, 15, 18, and 33 are amended and withdrawn claims 2, 34-38, 51-52. Claim 9 was canceled previously and claims 10, 14, 20, 24, 26-28, 31, 39, 44, 49, 54, 58-61, 64, 68, 72-75 and 81 were canceled therein. Applicants added new claims 86-89.

In the instant Supplemental Response claims 1, 6-8, 11-13, 15-19, 21-23, 25, 29-30, 32-33, and 71 remain pending and claims 2-5, 10, 34-38, 40-43, 45-48, 50-53, 55-57, 62-63, 65-67, 69-70, 76-80, and 82-85 remain withdrawn. New claims 86-89 previously presented in the April 28, 2010 response are canceled as redundant to claims 1 and 3-5. New claim 90 is added which corresponds to unintentionally canceled dependent claim 81. No new matter is added.

Supplemental amendments to the claims

Claim 1 is amended in the preamble and the screening and selecting method steps to include preparation of antibody fragments of the covalent and catalytic antibodies. This corresponds to claims 12 and 18 which both depend from claim 1 and limit the antibodies prepared in claim 1 to monoclonal antibodies or antibody fragments (claim 12) or single chain Fv fragments (claim 18). The specification also supports the preparation and isolation of antibody fragments at PP 0130 and in Examples VIII and IX in the specification.

Claim 1 also is amended in the preamble and the body of the claim to identify the catalytic antibodies or fragments thereof as those that "hydrolyze the peptide or protein" and to delete the descriptor "covalently bind to" as redundant. As such, the catalytic antibody screening and selecting step is correspondingly amended to recite "screening and selecting for antibodies that catalyze hydrolysis of one or more peptide bonds in the peptide or protein having an antigenic determinant contained in the pCRA ...". The term "comprising" is deleted and replaced with "contained in" because the pCRA might contain one or more, but not all of the antigenic determinants contained in the peptide or protein. The specification defines a catalytic antibody as one that requires at least covalent reactivity for catalytic activity, i.e., hydrolysis of peptides and release of product peptides (PP 0083). It is well known in the art that a peptide or protein may contain one or more antigenic determinants and one or more scissile bonds.

Claim 1 is amended further to delete the phrase "that reacts specifically with an antibody that binds to said antigenic determinant" that modifies the covalently reactive electrophilic group Y recited in the pCRA structure as it is functional language limiting the chemical structure. This claim language is best presented in the screening and selecting method step which encompasses identifying antibodies that covalently bind to the pCRA.

Claim 1 is amended further to correct grammar. In the pCRA structure the L1...Lx...Lm component is amended to recite "an" antigenic determinant because Applicants unintentionally deleted it when amending the claim in the April 28, 2010 response. Also, the recitation of "determinant" in the two screening and selecting steps is revised to the plural "determinants" to correspond grammatically with the previously included modifying phrase "one or more".

Claim 2 is amended in the preamble to recite "A water-binding, covalently reactive polypeptide antigen analogue (pCRA) of formula (1) or pCRAW:..." to clarify that the structure in claim 2 is a pCRA structure encompassed within the scope of amended claim 1. Claim 2 is amended to delete the phrase "a polypeptide" modifying antigenic determinant which was unintentionally added in the previous response of April 28, 2010. Claim 2 also is amended to delete the prefix "poly" from the phrase "polypeptide or protein" to correspond to amended claim 1. Claim 2 is amended further to delete the phrase "that reacts specifically with an antibody that binds to said antigenic determinant" that modifies the covalently reactive electrophilic group Y recited in the pCRA structure as it is functional language limiting the chemical structure. Thus, the structure of the water-binding pCRA or pCRAW, as it is designated, recited in withdrawn and amended claim 2 corresponds to the pCRA structure of amended claim where one of Y", Y' or Y contains the water-binding group as a terminal or internal component.

Claims 6-7 are amended to delete the phrase "and catalytic" in reference to antibodies resistant to dissociation by the recited denaturant. The specification discloses that covalent monoclonal antibodies, e.g., claimed monoclonal antibodies YZ-18, YZ-19, YZ-20, YZ-21, YZ-22, YZ-23 and YZ-24 are resistant to the denaturant SDS (PP 0046, 0073, 0201, 0526; Figs. 16, 42).

Claim 13 is amended to add the phrase "or peptide fragments" to the recited list of proteins from which the antigenic determinant of the pCRA is obtained. This amendment corresponds to the recitation in amended claim 1, from which claim 13 depends indirectly via claim 12, that the pCRA antigenic determinant is from a protein or peptide. Claim 13 also is amended to delete the redundant "is" before the term "comprises".

Claim 22 is amended to clarify that the "antibody fragments", as recited in amended claim 1 from which claim 22 depends, are fragments of IgG, IgM, IgD, IgA, or IgE.

Claim 33 is amended to clarify that the antigenic determinant is a pCRA antigenic determinant since claim 33 depends from claim 1.

Claims 34-36 are amended to correct grammar and recite that the monoclonal IgG "antibodies are" clones ..., etc.

Claim 38 is amended to replace "transonic" with "transgenic", and to delete the modifying term "antigenic" before pCRA as redundant. Claim 38 is amended further to recite "peptide or a protein" to correspond to the screening and selecting steps recited in amended claim 1. Claim 38 is amended further still to use the proper verb tense "selecting" in method steps b) and c).

Claims 40-43 are amended to recite the antibodies "or fragments thereof" to correspond to amended claim 38 which recites steps for screening, selecting and purifying the recited antibodies or antibody fragments.

Claims 46, 47 and 66 are amended to delete the term "immunoglobulin" and to recite "antibody" fragments to correspond to amended claim 38 from which the claims depend.

Claim 50 is amended to delete the term "immunoglobulin" and to recite "antibody" fragments to correspond to amended claim 38 from which the claims depend. Claim 50 also is amended to clarify that the screening step e) is screening for covalent binding to the peptide or protein containing one or more antigenic determinants comprising the pCRA to isolate the covalent antibody fragments. Claim 60 is amended further to clarify that the screening step f) is screening for catalytic hydrolysis of a peptide or protein containing one or more antigenic determinants comprising the pCRA to isolate the catalytic antibody fragments. These amendments correspond to the method steps b) and c) in amended claims 1 and 38 from which claim 50 depends indirectly and directly.

Claims 51-52 are amended to delete the second instance of "prepared" in the preamble as redundant.

Claim 56 is amended to recite that [L_1 . . . Lx . . . Lm] in the pCRA "comprises one or more" antigenic determinants because the pCRA in claim 1, from which claim 56 indirectly depends via claim 38 may comprise 1 to 1000 units (n is an integer from 1 to 1000). Claim 56 also is amended to include human, animal or plant peptide or proteins to correspond to claims 25 and 1 and cancer-associated peptide or protein (PP 0108) to correspond to claim 27.

Claim 57 is amended to recite that the pCRA "comprises one or more" antigenic determinants for the reasons as for claim 56. Claim 57 is further amended to include vasoactive intestinal peptide or epidermal growth factor which was recited originally in claims 59 and 61, respectively.

Claim 67 is amended to recite "pCRA" and not "pCRAW" in method step c) since claim 67 depends directly from claim 12 and indirectly from claim 1.

Claims 69-70 are amended to properly recite that the administered covalent or catalytic antibodies are "directed to" an antigen to correspond to claim 71 (PP 0110).

Claim 71 is amended to include "or antibody fragment" to correspond to the amendment to claim 1. Claim 71 also is amended to include hepatitis C virus protein E2 for immunotherapy of hepatitis infection (original canceled claim 72), beta.-amyloid peptide for immunotherapy of Alzheimer's disease (original canceled claim 73), epidermal growth factor receptor for immunotherapy of cancer (original canceled claim 74), or Factor VIII for immunotherapy of blood coagulation disorders (original canceled claim 75).

Claim 76 is amended in the preamble to properly recite that the covalent or catalytic antibodies produced by the method are "directed to" an antigen, as were claims 69-70 (PP 0110). Claim

76 also is amended to recite a pCRA "of claim 1" and to delete the improperly placed phrase "as of claim 1" in step a).

Claim 79 is amended in the preamble and the method steps a) to c) to delete the modifier "catalytic" before antibody. The specification discloses stimulating production of specific covalent and catalytic Abs and fragments thereof and methods for, *inter alia*, inhibiting these Abs for the treatment of a variety of medical diseases and disorders (PP 0023-0024, 0030). Claim 79 is further amended to limit the pCRA to "comprising one or more" antigenic determinants "to which the antibody is directed". The pCRA is defined, as in amended claim 1, as comprising 1 to 1000 units, i.e., n is an integer from 1 to 1000.

Claim 80 is amended to recite "medical disorder" instead of "disease state" to correspond to claim 70 from which claim 80 directly depends.

Claim 83 is amended to remove Markush language.

Claims 86-89 presented as new in the April 28, 2010 response are canceled as redundant. The scope of amended claim 1 encompasses a pCRA where the conformationally flexible moiety Y"-Y'-Y contains at Y", Y' or Y a water binding group. Therefore, all method claims entailing use of a pCRA also encompass use of a pCRA with the water binding group, i.e., all method claims encompass use of a pCRAW.

New claim 90 corresponds to unintentionally canceled original claim 81 and limits the autoimmune disease of claim 80 to systemic lupus erythematosus, systemic sclerosis, asthma, rheumatoid arthritis, mixed connective disease, Reiter's syndrome, Sjogren's syndrome, vasculitis, or bird shot retinopathy.

Thus, Applicants submit that these supplemental amendments correct claim language and Applicants' unintentional cancelation of dependent claims or claim elements of dependent claims that limit the specific proteins or peptides that contain the antigenic determinants comprising the pCRAs, including pCRAWs, of the instant invention and the specific medical disorders treatable by administration of the pCRAs. In addition, Applicants have amended the phraseology of withdrawn claims 2-5, 10, 34-38, 40-43, 45-48, 50-53, 55-57, 62-63, 65-67, 69-70, 76-80, and 82-85 and new claim 90, which is identical to canceled withdrawn claim 81, to correspond to that of the examined claims 1, 6-8, 11-13, 15-19, 21-23, 25, 29-30, 32-33, and 71 to strengthen Applicants' arguments that the withdrawn claims should not be restricted from prosecution with the currently examined claims. As further argued *infra*, Applicants submit that these supplemental amendments demonstrate that all the claims 2-8, 11-13, 15-19, 21-23, 25, 29-30, 32-38, 40-43, 45-48, 50-53, 55-57, 62-63, 65-67, 69-71, 76-80, 82-85, and 90 are dependent upon the basic method and pCRA structure of formula (1) encompassed by amended independent claim 1.

Restriction/Election of claims

The Examiner maintains the restriction of the claims such that claims 2-5, 34-70 and 76-85 remain withdrawn. The Examiner has rejected the Applicants contention that the original claims are unified by several technical features as described at length in Applicants' previous submission of 07/30/2009. The Examiner states that because **Taguchi** *et al.* teaches a CRA antigen having the same structure as Applicants' pCra, **Taguchi** *et al.* teach Applicants technical feature of conformational flexibility.

Applicants strongly aver that the pCRA of the instant amended independent claim 1 (and the pCRAW of amended withdrawn claim 2) and the conformational flexibility resulting from the structural arrangement provide the unifying feature of the claims. As discussed *infra* in traversing the §102 rejection over **Taguchi** *et al.*, the pCRA (and the pCRAW) are not identical to the CRA of **Taguchi** *et al.* Specifically, *inter alia*, the electrophile in the CRA of **Taguchi** *et al.* is not located at the functional group of an amino acid as in Applicant's pCRA. Instead, the electrophile of **Taguchi** *et al* is located at the C terminus. Moreover, the CRA of **Taguchi** *et al* does not contain a linker between the electrophile and the peptide C terminus. Without the linker, the electrophile in **Taguchi** *et al.* does not possess the requisite conformation flexibility provided to the electrophile in the instant pCRAs and pCRAWs. It is the pCRA (and pCRAW) structure, including the greater degree of conformational flexibility conferred by the combined side chain functional group-linker-electrophile unit, *per se*, that is the unifying element in claims 1-85.

Therefore, in view of the claim amendments and arguments presented *supra*, Applicants respectfully request that the Examiner reconsider the requirement for restriction and that the withdrawn claims 2-5, 34-38, 40-43, 45-48, 50-53, 55-57, 62-63, 65-70 and 76-80, and 82-85 be rejoined with the pending claims as Applicants have canceled claims 39, 44, 49, 54, 58-61, 64, and 81. Particularly, Applicants respectfully draw the Examiner's attention to claims 2-5 which encompass the pCRA structure of claim 1 including the optional water-binding group recited in claim 1. Also, Applicants wish to point out that claims 38 and 76 depend from claim 1 and recites a method for preparing the antibodies using the pCRA of claim 1 in an organism with autoimmune disease or medical condition, etc. by the method steps recited in original pending claim 12 and that claims 67, 84-85 depend directly or indirectly from claim 12, as originally filed. As such, claims 40-43, 45-48, 50-53, 55-57, 62-63, 65, 68, and 70 and claims 77-78 depend directly or indirectly from claims 38 and claims 76. Furthermore, claims 79-82 and 84 and new claim 90 utilize the pCRA in methods of treating medical conditions, such as autoimmune diseases. Thus, practice of the methods recited in the withdrawn claims all require the pCRA of amended independent claim 1.

Petition under 35 U.S.C. §1.144

Pursuant to 35 U.S.C. §1.144, Applicants submitted a petition from requirement for restriction prior to the instant supplemental response. In the petition Applicants respectfully petitioned

the Group 1600 Director to reconsider the requirement for restriction of the claims. Applicants submit that while these supplemental amendments put the claims in better condition for allowance, the specific claim amendments presented herein do not alter Applicants' arguments against restriction in the petition.

Objections to the claims

Claims 10, 14-15, 18, and 38 were objected to for the reasons described in the Office Action mailed October 28, 2009. Claim 14 was canceled previously. With the exception of claim 38, as explained *infra*, claims 10, 18 and 15 were amended to overcome the claim objections in the response submitted April 28, 2010.

Withdrawn claim 38 is objected to for reciting "transonic". Claim 38 is amended to replace "transonic" with "transgenic".

Accordingly, in view of these amendments, Applicants respectfully request that the objections to claims be withdrawn.

Applicants reiterate herein their arguments presented in the Response submitted April 28, 2010 to overcome the 35 U.S.C. §112, first and second paragraph, rejections and the 35 U.S.C. §102 rejections and include new arguments, if necessary, in view of the supplemental amendments to the claims described *supra*.

The 35 U.S.C. §112, second paragraph, rejections

Claims 1, 6-8, 10-33, and 71-75 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Applicants respectfully traverse these rejections.

The Examiner states that claims 1 and 11 are unclear in their recitation of covalent antibodies as it is unclear what is meant by covalent antibodies because claim 1 produces catalytic antibodies using pCRA which is what the antibodies are considered to be for examination purposes. The Examiner continues that Applicant's amendment of claim 1 is indefinite because it is not clear whether "...covalent antibodies that form complexes with polypeptide antigens..." is covalently bound or not.

Applicants have canceled claims 10, 14, 20, 24, 26-28, 31, and 72-75. As discussed *supra*, independent claim 1 is amended to delete the phrases in the preamble considered indefinite and to amend the preamble and the body to recite antibodies that bind a peptide or a protein covalently and catalytic antibodies hydrolyze the peptide or protein and to clarify in the body of the claim that both types of antibodies are prepared by the method. As discussed *supra*, dependent claim 11 is amended to recite that the covalent antibodies or catalytic antibodies screened and selected in steps a) and b) that are now amended into claim 1 are polyclonal antibodies.

Covalent and catalytic antibodies are functionally distinct entities. Covalent antibodies covalently bind naturally occurring peptide and protein antigens devoid of artificially incorporated electrophiles covalently. The binding by covalent antibodies is stable and resistant to dissociation to denaturants. Covalent antibodies do NOT express appreciable catalytic activity. Catalytic antibodies

initially form an unstable covalent intermediate with naturally occurring peptide and protein antigens devoid of artificially incorporated electrophiles. After a water molecule attacks the complex of a catalytic antibody and the peptide or protein antigen, the result is degradation of the peptide or protein antigen by the catalytic antibody.

pCRAs and pCRAWs of the present invention bind covalently to both types of antibodies, covalent antibodies, as well as catalytic antibodies. However, unlike naturally occurring peptide and protein antigens, catalytic antibodies do not degrade pCRAs and pCRAWs, because the complex is usually resistant to water attack. The definition of 'covalent antibodies' as used in the present invention is supported by Figs. 41- 42 which shows gp120 binding by antibodies produced by immunization with a pCRA. The immune complexes were not dissociated by sodium dodecylsulfate, indicating irreversible antibody binding due to a covalent reaction. Sodium dodecylsulfate is well known to dissociate non-covalent complexes. Also, the antibodies owe their covalent reactivity to their increased nucleophilic reactivity attained by immunization with electrophilic pCRAs (PP0008, 0525, 0526). The mechanism whereby pCRAs and pCRAWs induce production of covalent antibodies is supported at PP 0099 and the distinction between covalent antibodies and catalytic antibodies is clarified in PP 0083. Examples of covalent antibodies raised to two pCRAs are described at PP 0087. Applicants submit, therefore, that covalent antibodies and catalytic antibodies, as recited in the claims, is clearly defined and would be readily understood by one of ordinary skill in the art given the recitation in the claim and disclosure in the specification.

The Examiner states that claim 6 is indefinite in the recitation of "denaturant" as there is no antecedent basis for the term in claim 1. Secondly, the Examiner states that claim 6 depends from claim 1 which requires the complexes not to dissociate upon treatment with a protein denaturant. The Examiner concludes that claim 6, in reciting "resistant to dissociation" is broader than claim 1.

As discussed *supra*, the phrase containing "...do not dissociate on treatment with a protein denaturant" was deleted from amended independent claim 1, so, as a first instance, the recitation of "a denaturant" is proper. Applicants submit that the body of claim 1 is amended to recite that the antibodies produced by the method of claim 1 are, *inter alia*, effective to covalently bind to the peptide or protein or pCRA antigen determinant comprising the same. As such, claim 6 is amended as discussed *supra* to clarify that covalent antibodies binding to the peptide or the protein is further limited by being resistant to dissociation by "a denaturant". Thus, with the deletion of the phrase containing the recitation "do not dissociate on treatment with a protein denaturant", dependent claim 6 is not broader than amended claim 1.

The Examiner states that claim 13 is indefinite for reciting "the antigenic pCRA is the CRA derivative of gp120..." because it is unclear how the term "CRA derivative" is related to the formula (1). As discussed *supra*, amended claim 13, which now depends from claim 1, recites that the antigenic determinant of the pCRA comprises the recited proteins or peptide fragments thereof to correspond to claim 1 amendments. Thus, the claim clearly identifies specific peptide antigenic determinants.

The Examiner states that claim 14 is indefinite for reciting "the polypeptide" as there is no antecedent basis for "the polypeptide" in claim 12 from which this claim depends. Claim 14 was canceled.

The Examiner states that claim 18 is indefinite for reciting "single chain Fv fragments expressing covalent or catalytic activity. The Examiner is unclear how an Fv fragment expresses these activities and what is a covalent activity in relation to an Fv fragment. As discussed in the response filed April 28, 2010, the phrase "expressing covalent or catalytic activity" was deleted from the claim, as are method steps d) and e). Claim 1 is amended to recite antibodies or antibody fragments thereof screened and selected by the method will bind covalently to the antigenic pCRA or to a peptide or protein having the antigenic determinant comprising the pCRA and will catalytically hydrolyze the peptide or protein. As amended, claim 18 limits the antibody fragments to Fv fragments and describes how they are isolated.

Accordingly, in view of the amendments and arguments presented herein, Applicants respectfully request that the rejection of claims 1, 6, 11, 13-14, and 18 under 35 U.S.C. §112, second paragraph, are withdrawn.

The 35 U.S.C. §112, first paragraph, rejections

Claim 1 is rejected and claims 6-7, 11-12, 15-23, 25-29, and 71-75 remain rejected under 35 U.S.C. §112, first paragraph, written requirement. Applicants respectfully traverse this rejection.

The Examiner states the independent claim 1 is directed to a method of generating catalytic antibodies to a polypeptide covalently attached to any transition state analog of any reaction and injecting the antigen into any organism such that the antibodies produced show the catalytic activity of cleaving any peptide bond of any polypeptide. The Examiner continues that the specification does not disclose how catalytic antibodies produced against any pCRA comprising any polypeptide epitope can catalyze the cleavage of any peptide bond of any antigenic polypeptide. The Examiner concludes that given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Applicant has amended independent claim 1 to limit Y" to a linker as is disclosed in Fig. 4 and 48-49 and in paragraphs 0034-0035, 0079-0080, 0098, 0590, 0618. Claim 1 is amended to limit the antigenic determinant of a peptide or protein and to incorporate steps recited in dependent claims of screening for and selecting for antibodies or antibody fragments that both covalently bind the pCRA or a peptide or protein comprising the antigenic determinant thereof and catalytically cleave the peptide or protein as discussed *supra*. The specification well describes preparing covalent antibodies and catalytic antibodies using antigenic determinants from gp120, VIP, CD4, β-amyloid peptide 1-40 or β-amyloid peptide 1-42.

The specification describes that a linker, for example, but not limited to, a suberic acid or gamma-malelmidobutyryl group (Fig. 4) is placed between the electrophile Y and the side chain functional group of the antigenic determinant using known linker techniques (PP 0262) to enable control of the distance therebetween and the spatial positioning of these groups to provide conformational flexibility and freedom to permit simultaneous covalent binding of the Y electrophile to the antibody nucleophile and of the antigenic determinant to the antibody paratope (PP 0034, 0099). Optionally, the Y electrophile may be derivatized with a charged or neutral group, such as a (4-amidinophenyl)methylamine group, a 1-amino-4-guanidinobutyl group or an ethylamine group (Fig. 4) which provides an additional regulation of reactivity of the pCRA independent of the electrophilicity of Y (PP 0034).

In addition the specification discloses electrophiles, which as one particular example, generally are mono- or di-phenylphosphonates or boronates. The Figures (Figs. 5B-5C) disclose these structures and depict the phenyl(s) moiety as unsubstituted or substituted. The specification discloses that polypeptide analogs in which a covalently reactive electrophile can readily be located in side chains of the amino acids instead of the peptide backbone without unduly disturbing the native peptide or protein antigenic structure. (PP 0010). In general, as shown in Fig. 5A, the electrophile need only comprise an electron deficient atom (Z), which forms a covalent bond with the nucleophile and may contain one or more substituents (–R1 and –R2) attached to Z. R1 and R2 can be any atoms or groups that modulate the proclivity of Z to form covalent bond with a nucleophile. Typical examples of R1 and R2 include alkyl groups, alkoxyl groups, aryl groups, aryloxyl groups, hydrogen, and hydroxyl group. R1 and R2 can be pairs of the same or different substituents and R1 and R2 can be substituents that increase or decrease the covalent reactivity of the electrophile. The electronic characteristics of R1 and R2 control the electrophilic reactivity of the electrophile.

In general, the claimed pCRAs structures represent a broad genus unified by the common feature of covalent reactivity of the electrophile incorporated in the pCRAs with nucleophilic antibodies. Essentially all antibodies tested directed against diverse antigens express an innately occurring nucleophilic site with functional similarity to the serine protease family of enzymes. Consequently, the pCRAs react covalently with diverse antibodies, with specificity derived from noncovalent binding of the antigenic epitope of the pCRA to the traditional antibody paratope. Structural examples of pCRAs encompassing the entire genus that is reactive with covalent and catalytic antibodies directed to any antigen of claim 1 are provided in Example I for EGFR-pCRA, Example II for gp120-pCRA, Example III for VIP-pCRA and Example X for Aβ-pCRA.

In addition, the specification describes the induction of gp120 selective nucleophilic polyclonal antibodies in Example VI, the induction of VIP-selective nucleophilic polyclonal antibodies in Example VI, the induction of VIP-pCRA variant structures in Example XI, the structures of Aβ-pCRAs/pCRAWs and the antibody induction in Example X, covalent phage selection with gp120-pCRA:

Isolation of gp120 selective catalytic antibodies in Examples VIII, and specific inhibition of anti-VIP catalytic antibodies by VIP-pCRAin Example III.

Thus, the written description provides sufficient guidance for one of ordinary skill in the art to prepare covalently binding, catalytic antibodies to a antigenic polypeptide of medical interest. The pCRA can be synthesized using the described electrophiles and linkers to bond to appropriate functional groups in the peptide or protein antigenic sequence, immunization of an organism is well-known in the art and the subsequent screening and selecting for produced covalent antibodies and covalent and catalytic polyclonal or monoclonal antibodies or Fv fragments is well-described in the specification. It is well known in the art that near homologs or analogs of a chemical structural are likely to be functionally similar, if not identical. One of ordinary skill in the art is well-suited to design alternative linkers for the instant pCRAs based on the particular side chain functional groups L' and particular electrophile Y or, optionally, Y'-Y without undue experimentation and with a reasonable expectation of success. Similarly, it is known in the art that, *inter alia*, phosphonate or boronates are excellent electrophiles to covalently bind to nucleophilic antibodies. One of ordinary skill in the art is well able to design a suitable electrophile given the art and the disclosure of many electrophilic structures in the specification.

Therefore, the written description contained in Applicant's specification allows one of ordinary skill in the art to practice the invention of amended independent claim 1 and dependent claims 6-7, 11-12, 15-23, 25-29, and 71-75. Accordingly, in view of the amendments and arguments presented, Applicants respectfully request that the rejection of claims 1, 6-7, 11-12, 15-23, 25-29, and 71-75 under 35 U.S.C. §112, first paragraph, written description, be withdrawn.

Claim 1 is rejected and claims 6-7, 11-12, 15-23, 25-29, and 71-75 remain rejected under 35 U.S.C. §112, first paragraph, enablement requirement. Applicants respectfully traverse this rejection.

The Examiner states that the specification, while being enabling for a method of generating catalytic antibodies to the antigens of Figs. 36 or 48-49 or compounds of claims 30-33 where the method comprises administering the pCRA to an organism, such as a mouse, and where the catalytic antibodies cleave the peptide bond of gp120 peptide, does not reasonably enable a method of generating a catalytic antibody that shows proteolytic activity against any peptide bond of any protein or peptide. The Examiner continues that production of catalytic antibodies depends on the structure of the transition state analog and the enzymatic reaction depends on mimicking the transition state analog of bond cleavage or formation of that reaction. The Examiner concludes that the specification does not teach the structures of all the constituents of the pCRA recited in claim 1 and, hence, the transition state analog of peptide bond cleavage reaction, the specification does not enable any person skilled in the art to which it pertains or is most nearly connected to make and use the invention commensurate in scope with these claims.

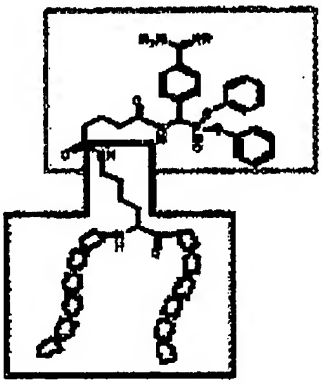
Applicant has amended independent claim 1 as discussed *supra*. Applicants maintain that the written description in the specification provides sufficient guidance for one of ordinary skill in the

art to prepare covalent antibodies or antibody fragments thereof and catalytic antibodies or antibody fragments thereof as recited in the method steps of amended independent claim 1. Applicants also submit that the enablement in the specification to prepare such antibodies to gp120, vasoactive intestinal peptide (VIP), epidermal growth factor receptor, β-amyloid peptide 1-40 or β-amyloid peptide 1-42 antigenic determinants, as described *supra*, enables one of ordinary skill in the art to prepare covalent antibodies and catalytic antibodies to other prophylactic or therapeutic antigenic polypeptides, such as, but not limited to, cytokines, growth factors, cytokine and growth factor receptors, proteins involved in the transduction of stimuli intiated by growth factor receptors, clotting factors, integrins, antigen receptors, enzymes, transcriptional regulators particularly those involved in cellular program, such as differentiation, proliferation and programmed cell death, control, other inducers of these cellular programs, cellular pumps capable of expelling anticancer agents, microbial and viral peptide antigens (PP 0137).

Independent claim 1 is amended to limit the antigenic determinant to a peptide or protein antigenic determinant. One of ordinary skill in the art must know the antigenic sequence of the peptide of interest, although Applicants submit that one of ordinary skill in the art could readily make a pCRA with a potential antigenic sequence where the isolation of covalently binding, catalytic antibodies would be an indicator that the tested polypeptide sequence is antigenic. As discussed, the specification describes the structural components of a pCRA and how to make the pCRA with appropriate electrophiles and linking molecules. Producing an antibody in an organism is well-known in the art and the specification describes and enables one of ordinary skill in the art to screen and select for covalently binding, catalytic antibodies or fragments thereof from serum or lymphocytes depending on whether one is screening for polyclonal or monoclonal antibodies or fragments.

As such, at a minimum the specification enables induction of gp120 selective nucleophilic polyclonal antibodies in Example VI, induction of VIP-selective nucleophilic polyclonal antibodies in Example VI, induction of VIP-pCRA variant structures in Example XI, the tructures of Aβ-pCRAs/pCRAWs and antibody induction in Example X, covalent phage selection with gp120-pCRA: Isolation of gp120 selective catalytic antibodies in Examples VIII, and specific inhibition of anti-VIP catalytic antibodies by VIP-pCRAin Example III.

Also, the enablement rejections appear to derive from the Examiner's assertions that the pCRAs and pCRAWs of the present invention are synonymous with transition state analogs (TSAs) described by Mader *et al.* Chem Rev. 1997, 97, 1281-1301. Applicants maintain that pCRAs/pCRAWs of the present invention are chemically and functionally distinct from the TSAs as described in detail in the Applicant's submission of 7/30/2009. The differences between TSAs and pCRAs are summarized in the Table below which clearly demonstrates that Transition State Analogs (TSAs) are not pCRAs/pCRAWs.

Feature	TSA Mader et al. Chem Rev. 1997, 97, 1281-1301	pCRA/pCRAW US 10/581294
Structure		
Chemical properties	• Full negative charge • No covalent reactivity • Reactive group within peptide backbone or terminus	• Covalent reactivity • Reactive group on peptide side chain
Properties of induced Antibodies	• *de novo* synthesis of Abs induced by oxyanion hole • Noncovalent TS stabilization • Esterase activity, no example of proteolytic activity	• Preferential recruitment of innate nucleophilic Abs coordinated with adaptive development of peptide specificity • Covalent catalysis, Proteolytic activity

The broad utility of pCRAs can be appreciated if it is understood that all antibodies tested were found to have nucleophilic sites that react with electrophiles in coordination with noncovalent binding of the antibody to the antigenic epitope or determinant (see Example 1). Therefore, pCRAs containing the appropriate electrophile and the appropriate antigenic epitope can be used broadly to identify any covalently binding antibody and any catalytic antibody to any peptide or protein antigen. Multiple examples of such covalently binding antibodies and catalytic antibodies are provided throughout the specifications. As described in the specifications, the pCRAs recruit the innate nucleophilic reactivity of antibodies and induce adaptive improvement of the nucleophilic reactivity coordinated with improvement of the noncovalent binding affinity for defined antigenic epitopes.

Chica *et al* Curr Opin Biotechnol, 1997, 97, 1281-1301 discuss difficulties in obtaining enzymatic activity by ab initio design and by directed evolution methods. The Examiner's enablement

rejections are based in part on the difficulties discussed by **Chica** *et al.* The present invention does not rely on the methods discussed by **Chica** *et al.* Therefore, the Applicants maintain that **Chica** *et al* is not germane to the present invention.

In addition, Applicants provided verification of enablement is available from additional examples of the utility of pCRAs published in scientific journals by the Applicants and other research groups as shown in the following outline. Copies of these references were submitted with the Response of April 28, 2010 and are not resubmitted herein.

I. Enablement of immunization/catalytic antibody induction

A. Immunization with pCRA

1. Induction of Induction of gp120 selective catalytic antibodies: Examples II and VI (**Paul** *et al.*, J Biol Chem 2003 May 30; 278(22):20429-20435).

2. Induction of gp120 selective covalent antibodies: Example VI (**Nishiyama** *et al*, J Mol Recognit. 2006 Sep-Oct; 19(5):423-31).

3. gp120 peptide CRA: Mol Immunol. 2009 Nov; 47(1):87-95. This paper reports catalytic antibody production by immunization of mice with a peptide CRA.

B. Immunization with V3 epitope pCRA

1. Induction of virus reactive covalent antibodies: Nishiyama *et al*, J Biol Chem. 2007 Oct 26; 282(43):31250-6.

II. Enablement of catalytic antibody selection/isolation

A. Covalent phage selection with Aβ-pCRA: Isolation of Aβ selective catalytic antibodies: **Taguchi** *et al*, J Biol Chem. 2008 Dec 26; 283(52):36724-33.

B. Aβ CRA: **Kasturirangan** *et al*, Biotechnol Prog. 2009 Jul-Aug;25 (4):1054-63. This paper reports isolation of Aβ selective catalytic antibodies by covalent phage selection.

III. Enablement of catalytic antibody selection/isolation

A. Specific Inhibition of anti-VIP catalytic antibodies by VIP-pCRA: Example III (**Nishiyama** *et al.*, J Biol Chem 2004 Feb 27; 279(9):7877-83).

B. Specific Inhibition of anti-FVIII catalytic antibodies by FVIII-pCRA and FVIII-C2-pCRA: **Planque** *et al.*, J Biol Chem. 2008 May 2; 283(18):11876-11886.

Thus, the specification enables amended independent claim 1. As claims 6-7, 11-12, 15-23, 25-29, and 71-75 depend directly or indirectly from amended claim 1, these dependent claims also are enabled. Accordingly, in view of the amendments and arguments presented herein, Applicants respectfully request that the rejection of claims 1, 6-7, 11-12, 15-23, 25-29, and 71-75 under 35 U.S.C. §112, first paragraph, enablement, be withdrawn.

The 35 U.S.C. §102 rejections

Claim 1 is rejected and claims 8-14, 16, 24, and 31 stand rejected under 35 U.S.C. §102(a) as being anticipated by **Taguchi** *et al.* (Bioorg. and Med. Chem. Lett., 2002, 12:3167-3170). Applicants respectfully traverse this rejection.

The Examiner states that **Taguchi** *et al.* teach catalytic antibodies raised by using a gp120 polypeptide epitope (L of claim 1 having a carboxyl functional group of amino acid residues as Y") attached covalently to a phosphonate ester (Y reactive electrophilic group, Transition state analog) which comprises a covalently reactive antigen (CRA) (pg. 3168, Fig. 1) where the phosphonate ester moiety binds to the antibody. The Examiner also states that **Taguchi** *et al.* disclose a method of producing the antibody by administering the CRA to a mouse (pg. 3168, col. 1, PP 3).

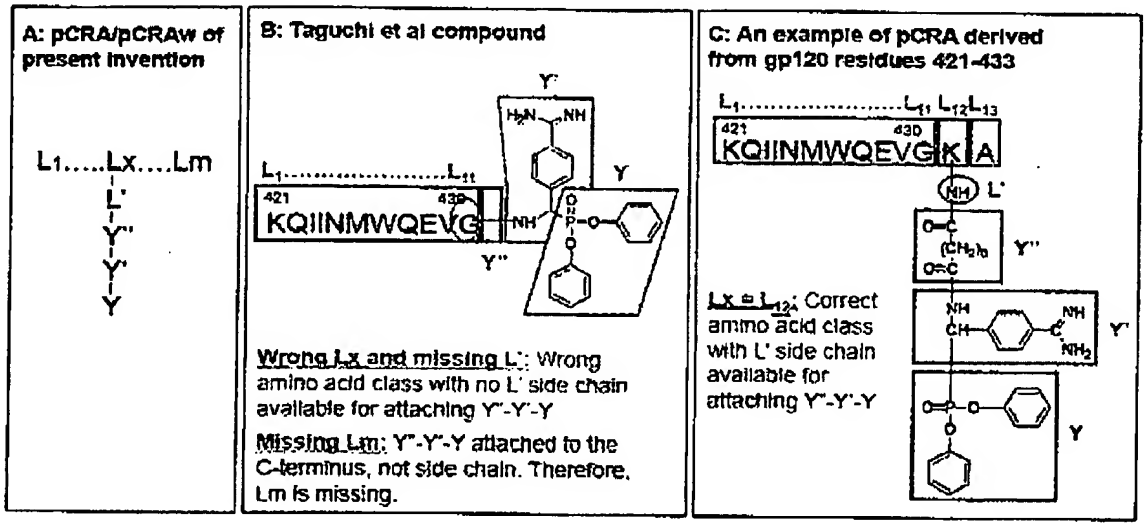
Applicants submit that **Taguchi** *et al.* disclose an antigenic peptide analog consisting of HIV gp120 residues 421-431 with a diphenyl amino(4-amidinophenyl)methanephosphonate located at the C-terminus. Antibodies to the peptide determinant recognized the peptidyl phosphonate probe.

Claims 9-10, 14, 24 and 31 are canceled. As discussed *supra*, independent claim 1 is amended to recite a Y" linker. Also, claim 1 is amended to incorporate steps to obtain, screen and select for the covalent antibodies and catalytic antibodies or the antibody fragments of either produced by the pCRA in the organism.

It is well established that to anticipate a claim, a single reference must disclose each and every claim element as they are arranged in the claim. The Examiner maintains that, in the CRA of **Taguchi** *et al.*, the gp120 polypeptide epitope is the "L" in Applicant's pCRA where the carboxyl functional group of the amino acid residue corresponds to L' in the pCRA. As recited in amended independent claim 1, the L1...Lx...Lm component of Applicants' pCRA is an antigenic determinant of a peptide or a protein where L' within the antigenic determinant is a functional group of any amino acid side chain, e.g., those of Lys, Asp, Glu, Cys, Ser, Thr, and Tyr (PP 0095). L' is linked by a linker Y", for example, but not limited to, a suberic acid or a gamma-maleimidobutyryl group directly to the electrophilic group Y or L' is indirectly linked to Y" via the optional Y' group (which may be the 4-amidinophenyl)methylamine group as in **Taguchi** *et al.*) to the electrophilic group.

At a minimum Applicants submit that the CRA of **Taguchi** *et al.* does not have a Y" group as in Applicants' claim 1. Applicants present the diagram below to explain their position. Panel (A) shows the general formula for pCRAs of the present invention. Panel (B) shows the compound disclosed in **Taguchi** *et al*, an analog of gp120 residues 421-433. This compound consists of a peptide corresponding to residues 421-431, in which the backbone carboxyl group of Gly431 is connected to the aminoalkylphosphonate group via a C-N covalent bond. The chemical designation system identifying the pCRA elements in the present invention is employed to identify various components of the **Taguchi** *et al* compound. Panel (C) shows an example pCRA of the present invention corresponding to gp120 residues 421-433. Element Lx in the **Taguchi** compound is devoid of a side chain and cannot be used prepare a pCRA of the present invention, as a defining feature of the pCRAs is the side chain location of

the unit composed of elements L'-Y"-Y-Y. Moreover element L' of the present invention is missing altogether in the **Taguchi** *et al* compound. Moreover, element Lm is also missing in **Taguchi** *et al* compound, as the unit composed of elements Y"-Y'-Y is attached to the C-terminus. In comparison, the unit of elements Y"-Y'-Y is attached to the side chain in the pCRAs, making possible incorpopration of element Lm in the present invention. The lack of chemical identity between the **Taguchi** *et al* compound and the pCRAs of the present invention is evident.



For these reasons, neither can **Taguchi** *et al.* render obvious amended independent claim 1 and, by extension, dependent claims 8, 11 and 16. Given the synthetic and structural requirements for the CRA of **Taguchi** *et al*, one of ordinary skill in the art cannot predict that modifying any side chain functional group with a linker and electrophile would produce an effective pCRA because such positioning would not mimic the Lys432-Ala433 cleavage target in gp120. In the CRA in **Taguchi** *et al.*, the positively charged amidino group adjacent to the phosphonate diester group serves as an analog of Lys432 (pg. 3167, 2nd col., last PP).

Thus, Applicants' pCRA as recited in claim 1 is arranged differently from and comprises components not found in the CRA disclosed in **Taguchi** *et al.* In the absence of these teachings, **Taguchi** *et al.* do not teach all the claim elements of the pCRA of amended independent claim 1 as they are arranged and, therefore, cannot anticipate the method recited in amended independent claim 1. Claims 8, 11-13 and 16 depend directly or indirectly from amended independent claim 1 and as claim 1 is not anticipated by **Taguchi** *et al.*, these dependent claims are also not anticipated by **Taguchi** *et al.* Accordingly, in view of the arguments and amendments presented herein, Applicants respectfully request that rejection of the claims 1, 8, 11-13, and 16 under 35 USC §102 be withdrawn.

Claim 1 is rejected and claims 8-14, 16-18, 21-22, 24-29, 71-72, and 74 stand rejected as being anticipated by **Paul** *et al.* (U.S. Patent No. 6,235,714). Applicants respectfully traverse this rejection.

In considering independent claim 1, the Examiner states that **Paul** *et al.* teach a catalytic antibody and a method of producing said antibody (monoclonal or polyclonal, single chain Fv fragments; col. 16, ll. 48-66) by administering to an organism (MRL/lpr mouse, col. 14, ll. 45-60) a covalently reactive peptide antigen, CRAA (col. 3, ll. 25-45) where the CRAA is X1-Y-E-X2, where X1 and X2 are peptide molecules having reactive functional group attached to and electrophonic reactive center E that reacts covalently to a nucleophile, and Y is a basic residue of the peptide molecule. The Examiner maintains that the CRRA of **Paul** *et al.* is identical to Applicants' pCRA. The Examiner also states that **Paul** *et al.* teach that the antigen molecule comprises tumor necrosis factor, epidermal growth factor receptor, gp120 (claim 4), etc. and that **Paul** *et al.* disclose that the catalytic antibodies produced against the antigens can be used for the treatment of medical disordes like cancer, autoimmune disease (col. 6, ll. 1-13; Figs. 19A-19B.

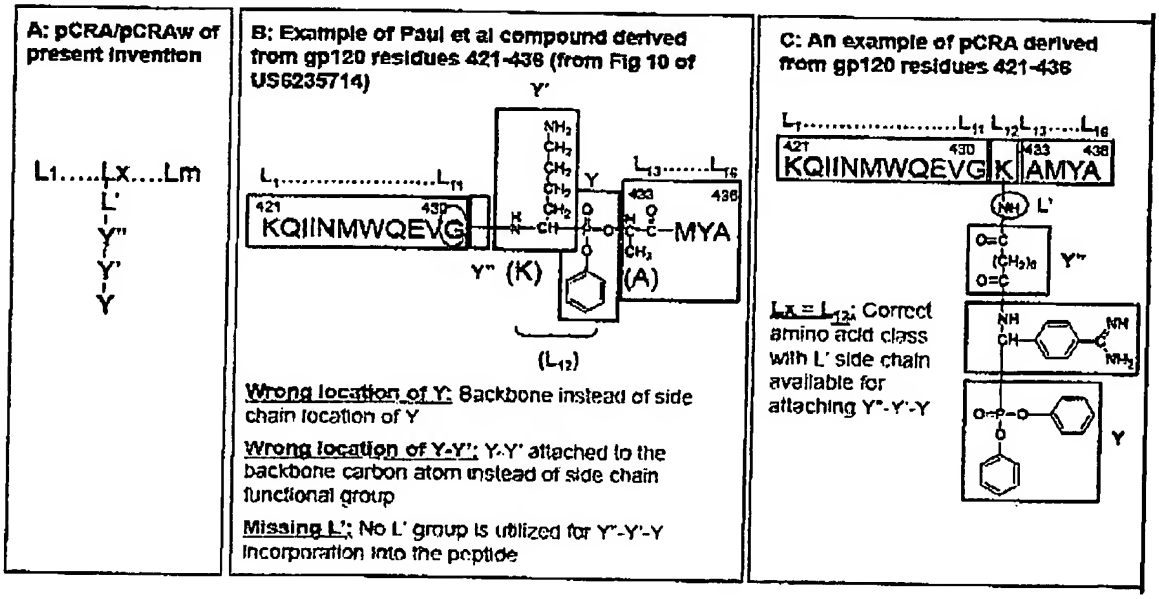
Applicants submit that **Paul** *et al.* disclose covalently reactive antigen analogs (CRAA) that stimulate production of catalytic antibodies specific for predetermined antigens that are associated with certain medical disorders. The CRAA has a X1-Y-E-X2 component structure where E is an electrophilic reaction center, Y is a basic residue (Arg or Lys) at the first amino acid on the N terminal side of the reaction center or at the P1 position and X1 and X2 are three to ten flanking amino acids on the N-terminal and C-terminal side of the reaction center (col. 3, ll. 26-35).

Applicants have canceled claims 9-10, 14, 24, 26-28, 72, and 74. Applicants' amended independent claim 1 is described *supra*. It is well established that to anticipate a claim, a single reference must disclose each and every claim element as they arranged in the claim. Applicants strongly maintain that, the Examiner's contention notwithstanding, Applicants' pCRA, as recited in amended independent claim 1, is **not** (Applicants' emphasis) identical to the CRAA of **Paul** *et al.* Applicants' pCRA contains a covalently reactive electrophilic group, such as a mono- or di-substituted phosphonate or boronate group that is linked to an amino acid side chain functional group via a linking moiety, e.g., *inter alia*, a gamma-malimidobutyryl group or a suberic acid group. In addition, optionally, the pCRA may comprise a charged or neutral group between the phosphonate/boronate moiety, e.g. and the linker, as shown in Fig. 4. As such, the side chain functional group may comprise any amino acid, e.g., the negatively charged carboxyl of aspartic acid or glutamic acid, the positively charged amino group of lysine or arginine, the hydroxy group of polar amino acids serine, threonine and tyrosine or the nonpolar sulfhydryl of cysteine (Fig. 4).

In distinct contrast, **Paul** *et al.* disclose that the CRAA described therein is composed of an electrophilic phosphonate ester flanked by amino acid residues, e.g., EGFR residues 294-303 on the N terminal side and EGFR residues 304-310 on the C terminal side (col. 15, ll. 5-8; Fig. 4). In addition the N terminal residue must be positively charged which limits the amino acids to arginine or lysine

(claim 1, Fig. 10). The phosphonate residue is inserted between residues in the polypeptide, but does not form bonds with any of the sidechain molecules (Figs. 15-17).

More particularly, Applicants present the figure below to explain their position. Panel (A) shows the general formula for pCRAs of the present invention. Panel (B) shows an example of the CRAA disclosed by **Paul** *et al*, an analog of gp120 residues 421-436. This compound consists of a peptide corresponding to residues 421-436. The chemical designation system identifying the pCRAs in the present invention is employed to identify various components of the CRAA disclosed by **Paul** *et al*. Panel (C) shows an example pCRA of the present invention corresponding to gp120 residues 421-433. Elements Y", Y' and Y of the pCRAs of the present invention are located within the peptide backbone of the **Paul** *et al* CRAA. In contrast, these elements are located on the side chain of an amino acid in the pCRAs of the present invention. The L' element of the present invention is missing altogether in the **Paul** *et al* CRAA. The lack of chemical identity between the **Paul** *et al* CRAAs and the pCRAs of the present invention is evident from this comparison.



The Applicants wish the Examiner to please note that the chemical designations from the present pCRA/pCRAW are used to illustrate chemical non-identity in panel B (L1...L11, Y", Y').

For these reasons neither can **Paul** *et al.* render obvious amended independent claim 1 and, by extension, dependent claims 8-14, 16-18, 21-22, 24-29, 71-72, and 74. Given the structural requirements for the CRAA of **Paul** *et al*, one of ordinary skill in the art cannot predict that modifying any side chain functional group with a linker and electrophile would produce an effective pCRA because such positioning would removes the electrophile from the flanked position at the reaction center within the peptide and require that a linker be incorporated to link the electrophile to the side chain functional

group. In the CRAA in **Paul** *et al.*, the specific positional combination of individual structural elements act in concert to (a) bind chemically reactive serine residues encoded by the germline genes for certain serine protease types of catalytic antibodies; (b) utilize ion pairing and noncovalent forces to bind structures such as positively charged Asp/Glu residues that are responsible for the basic residue cleavage specificity of the germline encoded catalytic sites; and (c) bind antibody combining sites at multiple amino acids via ion pairing and noncovalent force (col. 3, ll. 27-45).

Thus, Applicants aver that Applicants' pCRA as recited in claim 1 is not identical to the CRAA disclosed in **Paul** *et al.* **Paul** *et al.* do not teach all the claim elements of the pCRA of amended independent claim 1 as they are arranged and, therefore, cannot anticipate the method recited in amended independent claim 1. Claims 8-14, 16-18, 21-22, 26-29, and 71depend directly or indirectly from amended independent claim 1 and as claim 1 is not anticipated by **Paul** *et al.*, then neither would these dependent claims be anticipated by **Paul** *et al.* Accordingly, in view of the arguments and amendments presented herein, Applicants respectfully request that rejection of the claims 1, 8, 11-13, 16-18, 21-22, 25, 29, and 71 under 35 USC §102 be withdrawn.

Double patenting rejections

Claims 1, 6-29 and 71-75 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,855,528. The Examiner contends that U.S. Patent No. 6,855,528 teaches a method of producing a catalytic antibody (CRAA) which is identical to Applicant's pCRA.

Applicants have canceled claims 9-10, 14, 20, 24, 26-29 and 72-75. Claim 1 in U.S. Patent No. 6,855,528 does not provide the structure of the CRAA, however this patent is a divisional of U.S. Patent No. 6,235,714 which is cited as anticipating Applicants' independent claim 1 under 35 U.S.C. §102(b). As discussed *supra*, Applicant's pCRA is distinctly and structurally different from the CRAA. Nor, given the requirements for a CRAA, would Applicants' pCRA be an obvious variant thereof, particularly since the electrophilic group must be flanked by residues of the antigenic determinant and the N terminal residue must be positively charged overall. One of ordinary skill in the art cannot reasonably predict that linking a side chain functional group of any amino acid to the electrophilic group with the Y" groups would yield an effective polypeptide covalently reactive analogs (pCRA). Thus, Applicants' submit that a terminal disclaimer is not required. Accordingly, in view of the arguments and amendments presented herein, Applicants respectfully request that rejection of the claims 1, 6-8, 11-13, 15-19, 21-23, 25, 29 and 71 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,855,528 withdrawn.

Applicants submit that this Response supplemental to the Response submitted April 28, 2010 to the Office Action, mailed October 28, 2009, is complete. If any issues remain outstanding, please telephone the undersigned attorney of record for resolution. Applicants believe no fees are due,

however, should Applicants err, please debit any applicable fees from Deposit Account No. 07-1185, upon which the undersigned is allowed to draw.

Respectfully submitted,

Date: May 12, 2010

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